Thiamine Deficiency and Experimental Cardiac Necrosis[1] (35132)

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The effects of various environmental conditions and interventions on the severity of experimentally-induced myocardial infarct-like necrosis have been investigated by many workers. Changes in temperature (1), altitude acclimatization (2), muscular exercise (3), pretreatment with isoproterenol (4–6), body composition (7), species, strain, and age of the animals (8, 9) have all been correlated with the extent of damage resulting from the necrogenic effect of heavy doses of isoproterenol.

Cardiovascular disorders have been shown to accompnay nutritional deficiencies (10, 11); the most specific of these is the syndrome resulting from severe thiamine deficiency (12–14). We undertook this study to investigate the effect of necrotizing doses of isoproterenol on hearts of rats subjected to a moderate thiamine deficiency in which overt symptoms of the deficiency had not yet developed.

Methods. Male rats of the CFE strain (Carworth Farms) weighing approximately 150 g were divided randomly into two groups. One group was fed a complete purified diet and the second was fed an identical diet from which thiamine had been omitted.

After 15 days of feeding, experimental myocardial necrosis was induced with isoproterenol according to the technique described by Rona *et al.* (15). Subcutaneous injections of 80 mg of isoproterenol/kg of body weight were administered on 2 consecutive days at 24-hr intervals. On the third day the animals were sacrificed. The hearts were removed under chloroform anesthesia, and the extent of necrosis was evaluated macroscopically. The scheme devised by Rona *et al.* (15) was used to assess the degree of cardiac damage (0, no necrosis; 1, diffuse paling of the tip; 2, limited necrosis of the tip; 3, necrosis of the tip reaching up to a third of the left ventricle; 4, more than half of the left ventricle affected by necrosis).

The hearts from six animals on each diet not injected with isoproterenol were also evaluated.

Results. Growth curves (Fig. 1) of control and thiamine-deficient animals followed the pattern observed by other workers (16). Both groups of rats grew at the same rate for approximately 10–12 days. At this time the body weight of the control animals continued to increase while the animals fed the thiamine-free diet reached a plateau. No external signs of thiamine deficiency were seen in these animals, nor was food intake for the 2-week period significantly different from that of the controls. Following the first injection of isoproterenol both groups lost approximately 5% of their body weight. This was due in part to a reduction in food intake accompanied by a marked diuresis induced by the drug. These observations are in accord with those reported by other workers (17, 18). Following the second injection of the drug no further body weight loss was observed.

Contrary to our expectations, the myocardium of the thiamine-deficient rats was markedly resistant to the necrogenic effects of isoproterenol. The hearts of the animals fed the basal diet had a mean necrogenic rating of 3.2, as compared to 0.8 for the animals on the thiamine-deficient diet (Table I). The difference between these two values

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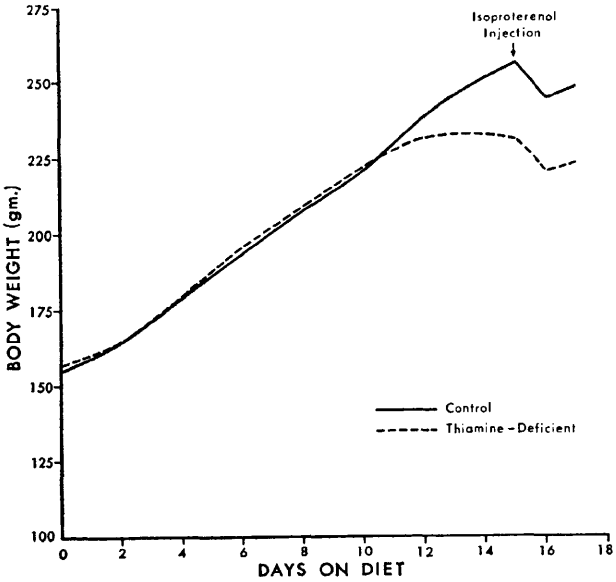

FIG. 1. Growth curves of control and thiamine-deficient rats.

is significant at the .01 level. The myocardium of noninjected animals on the basal diet was free from necrosis. One spontaneous infarct was observed in a thimaine-deficient animal that had not been injected with isoproterenol.

The distribution of the necrosis is detailed in Table II. All of the animals on the control diet suffered some cardiac necrosis as a result of treatment with isoproterenol. The hearts of over 75% of these animals sustained massive infarcts which were scored 3 or 4. Only 60% of the animals on the thiamine-deficient diet suffered cardiac necrosis, and over 90% of these were slight and scored as 1 or 2. The hearts of the animals which were not injected and maintained on a control diet were free of necrosis. Although one heart of a noninjected animal on the thiamine-deficient diet experienced a moderate infarct, we believe that this was due to chance and is not a significant finding.

Three animals on the basal diet died after the first injection of isoproterenol. There was no mortality among the animals on the thiamine-deficient diet.

Discussion. The results obtained in this series of experiments were surprising. We had expected that animals subjected to a moderate thiamine deficiency would be more susceptible to the necrogenic activity of isoproterenol. However, at least one other report has appeared which indicates that hearts from thiamine-deficient animals may be resistant to necrogenic stimuli. Follis (19) reported that cardiac necrosis produced by potassium deficiency was prevented if the animals were subjected to both potassium and thiamine deficiencies concurrently.

TABLE I. Mean Body Weight and Necrotic Ratings of Control and Thiamine-Deficient Rats.

Treatment	No. of rats	Body wt (g)	Necrotic rating
Isoproterenol injected			
Basal diet	16	249	3.2
Thiamine-free diet	20	224	0.8
Noninjected			
Basal diet	6	255	0
Thiamine-free diet	6	226	0.3

The reason for the apparent resistance of the hearts of thiamine-deficient rats to the necrosis induced by low postassium diets or isoproterenol is unclear. Metabolic changes in cardiac tissue which result from thiamine deficiency include a reduction in transketolase activity which occurs as early as the fourth day of feeding a thiamine-free diet (20). Within a week there is a reduction in

TABLE II. Distribution of Necrotic Ratings of Control and Thiamine-Deficient Rats.

Treatment	No. of rats	Ratings					No. of rats died
		0	1	2	3	4	
Isoproterenol injected							
Basal diet	16	—	1	1	4	7	3
Thiamine-free diet	20	8	9	2	1	—	0
Noninjected							
Basal diet	6	6	—	—	—	—	0
Thiamine-free diet	6	5	—	1	—	—	0

pyruvate and α-ketoglutarate dehydrogenase activity (16). The resulting block of ATP availability from TCA cycle oxidation led Wu *et al.* (21) to suggest that there might be an increased reliance on glycolytic ATP synthesis in the heart muscle of thiamine-deficient rats. It is noteworthy that these workers reported increased glycolytic activity as indicated by an initial increase in extramitochondrial α-glycerophosphate activity which returned to control levels within 4 to 5 weeks on the thiamine-free diet. If these results can be applied to the present study, it may provide a basis for a reasonable explanation for the unexpected resistance of our thiamine-deficient animals to the necrotic effects of isoproterenol.

Massive doses of isoproterenol elicit myocardial infarct-like necrosis by inducing a myocardial ischemia (22, 23). During the ischemic period the limitation of oxygen availability to the metabolizing myocardium results in a depression of oxidative metabolism and a consequent reduction in ATP produced via this pathway. It is conceivable that the myocardium from the moderately thiamine-deficient animal has an increased capacity for anaerobic glycolysis so that during the brief ischemia induced by isoproterenol enough ATP could be generated to maintain cellular integrity. Thus, when oxygen was again made available the cardiac tissue from these animals could resume normal function with cellular damage at a minimum.

Studies are being continued to investigate the resistance of the myocardium of animals which have been subjected to thiamine deficiency for prolonged periods of time.

Summary. Hearts of animals subjected to a moderate thiamine deficiency were resistant to the necrogenic effect of isoproterenol which at the dose level used (80 mg/kg of body wt) produced massive infarcts in animals fed a normal control diet. The reason for the apparent protective effect is unclear. It is postulated that cardiac tissue from rats in early thiamine deficiency may have an increased capacity for anaerobic glycolysis, as part of the metabolic response to a decrease in the activity of enzymes essential for oxidative phosphorylation. This capability is not shared by cardiac tissue from control animals.

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